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Initial clinical experience with radium 223: Case based series with review of the literature

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Introduction

The incidence of prostate cancer in Bulgaria is steadily increasing over the last few decades [1,2]. While the therapeutic strategy for hormone sensitive prostate cancer is well established, Metastatic Castration-Resistant Prostate Cancer (mCRPC) is still a challenge with an average life span of not more than two years [3]. Nevertheless, treatment options in this setting have emerged considerably during past ten years and showed significant improvement in survival rates compared to the pre-existing palliative regimens [4-6]. Since 2010 several new FDA and EMA approved medications entered clinical practice including enzalutamide and a birater one acetate which are new generation Androgen-Receptor Targeting Agents (ARTA) [7,8], sipuleucel-T, stimulating immune system [9], cabazitaxel – chemotherapeutic agent [10] olaparib, which is Poly (ADP-ribose) polymerase inhibitor [11] and radium 223 dichloride, used for radionuclide therapy [12]. However, more than 90% of patients with mCRPC have radiologic evidence of bone metastases, which are a major cause of death, disability, decreased quality of life, and increased treatment cost [13,14]. Currentbone-targeted therapies have not been shown to improve survival, and the benefits derived from bisphosphonates, RANKL inhibitors and existing radioisotopetreatments are limited to pain relief and delay of skeletal events [15]. In the last decade Radium-223 dichloride has been proved to be the first new generation osteotropic agent with a real clinical impact on survival in CRPC patients with metastatic bone disease [16].

The aim of this study is to present our initial experience in the application of Radium- 223 in mCRPC patients with symptomatic bone metastases as well as to demonstrate the clinical advantages of the different nuclear medicine and hybrid imaging modalities for the staging and therapeutic response evaluation in these patients.

Material and methods

For a time period of two years months we admitted four patients with metastatic castrate-resistant prostate cancer aged 50 –77 y in the Nuclear medicine department. All of them had symptomatic bone metastases and weretreated with Radium -223 dichloride. The standard clinical protocol included four intravenous applications with radioactivity of 55 kBq/kg in four weeks intervals. The product was delivered in a ready-to-use form, containing 6 ml with a radioactive concentration of 1100 kBq/mL (27 µCi/ml). Prior to injection the dose itself was calculated according to patient's BMI, date of release and the radioactive decay coefficient. In addition prior to every subsequent intravenous application a special attention to patients' blood count was paid and mainly to neutrophils, thrombocytes and hemoglobin levels.

The therapeutic response was summarized after integrated evaluation of all clinical and imaging data, including functional evaluation scale (Prostatetotal score and the EuroQoL 5 D utility). Serum Prostate Specific Antigen (PSA) levels were measured every month. In three out of four patients a baseline whole-body 99mtc Methylene Diphosphonate (MDP) bone scintigraphy was performed and repeated after the fourth application of Radium-223. The remaining one patient had a baseline and response evaluation imaging with positron emission tomography/ computed tomography using 68Ga labelled Prostate Specific Membrane Antigen (68 Ga PSMA PET/CT).

Results

The **first clinical case** was of a patient with high-risk prostate cancer (pT3bN0M0, PSA-39 ng/ml, Gleason score 8), diagnosed in the beginning of 2015. Androgen deprivation therapy with non-steroid antiandrogen (Bicalutamide, 50 mg per day) and Luteinizing Hormone Release Hormone (LHRH) agonists was initiated for a time period of four months and during this period the PSA levels decreased significantly reaching 0.003 ng/ml. The first admission of the patient to the nuclear medicine department was for staging and diagnostic evaluation. A Whole-Body Bone Scintigraphy (WBS), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) were performed consistently for staging and restaging purposes (Figures 1-4). None of the results definitely confirmed the presence of metastatic bone lesions so that in April 2015 the patient was scheduled for laparoscopic radical prostatectomy with regional lymph node dissection. Soon after (August 2015), serum PSA levels started rising again up to 0,7 ng/ml. Pelvic MRI doesn't revealed signs of local recurrence. Two consecutive PET/CT exams were performed using two different radiopharmaceuticals -18F Flourodeoxyglucose (FDG) known as universal tumortropic agent (Figure 5), and 18 F Choline, known as prostate-specific tumortropic agent (Figure 6). Results from both exams showed no evidence for local recurrence nor distant metastases. Nevertheless, External Beam Radiation Therapy (EBRT) of the prostatic bed is performed using daily radiation dosage 2 Gyuntil total radiation dosage of 66 Gyin September 2015. Despite EBRT and antiandrogen therapy PSA level continued rising up to 14.81 ng/ml with testosterone level of less than 0,16 nmol/l and negative imaging results. Treatment with a second-generation antiandrogen Enzalutamide (160 mg/daily) was imitated.

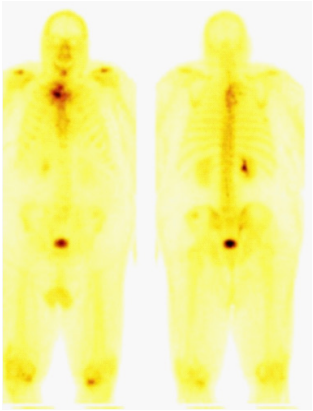

Figure 1: Whole-body bone scintigraphy with 99 m Tc MDP in patient №1 in January 2015, interpreted as insignificant inclusion of radiopharmaceuticals in the upper spine, more likely of degenerative / reactive origin, without convincing evidence of lesions in connection with the underlying disease.

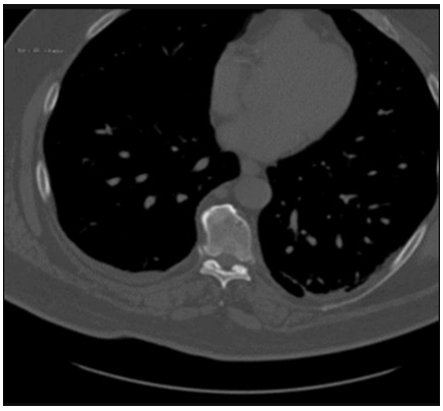

Figure 2: Computed tomography of the chest in patient №1 (January 2015) - data on degenerative changes in the thoracic spine, without bone lesions, suspected secondary.

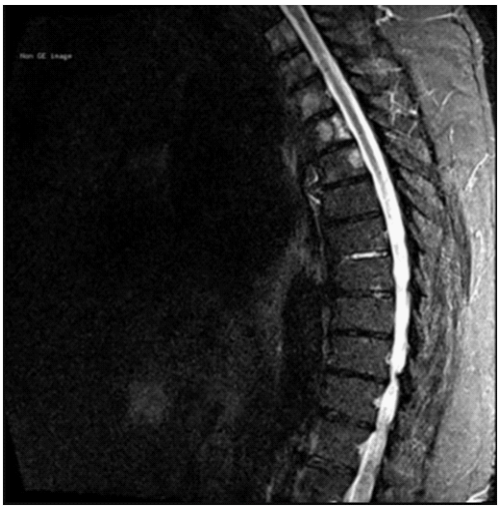

Figure 3: MRI of the spine in patient №1 (January, 2015) - areas with increased signal enhancement in the bodies of Th1-Th5.

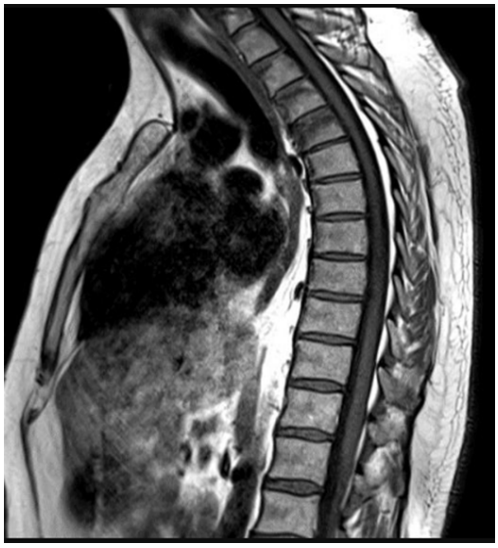

Figure 4: MRI of the spine in patient №1 (March, 2015), after completion of corticosteroid therapy, without convincing evidence of areas with pathological signal in the torsion vertebrae and possibly complete reversal of the changes.

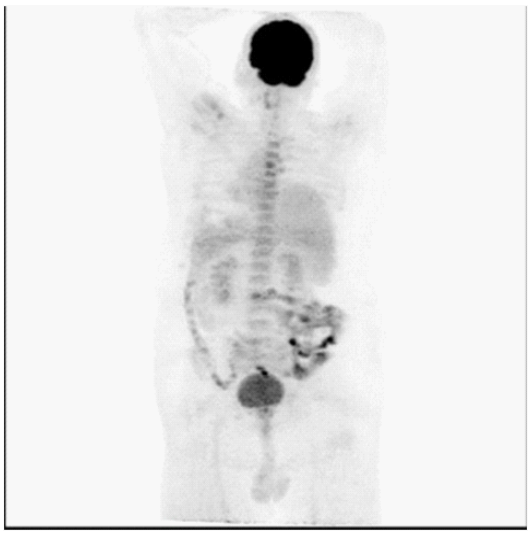

Figure 5: FDG PET / CT in patient №1, July 2015 - weak to insignificant inclusion of radiopharmaceuticals in Th 2-5 vertebrae, no evidence of underlying structural changes, suspected meta, inconclusive evidence of dissemination of the underlying disease; DD: post-inflammatory changes.

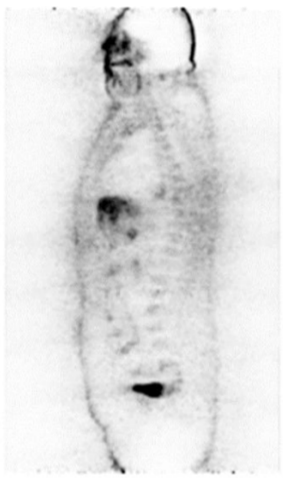

Figure 6: Choline PET, August 2015 - no data for areas with pathological fixation of radiopharmaceuticals.

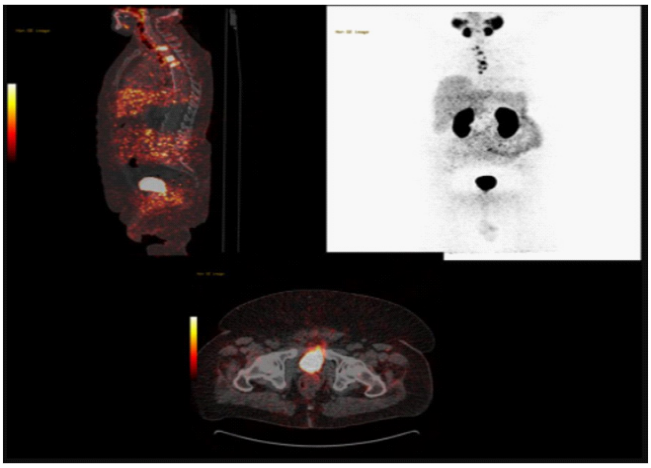

Figure 7: 68 Ga PSMA PET / CT in patient №1, March, 2016 - focal and intensive accumulation of the radiomarker in the thoracic vertebrae, without morphological substrate, corresponding to dissemination of the underlying disease, without evidence of local recurrence.

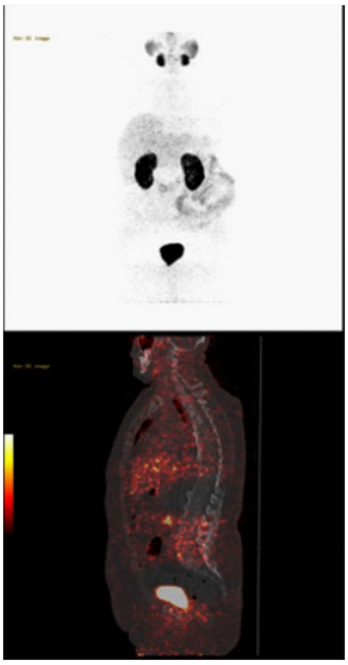

Figure 8: Ga PSMA PET / CT in patient №1, September, 2016, after 4 applications of 223 Radium - complete response from therapy, no data for other areas with pathological fixation of the radiomarker.

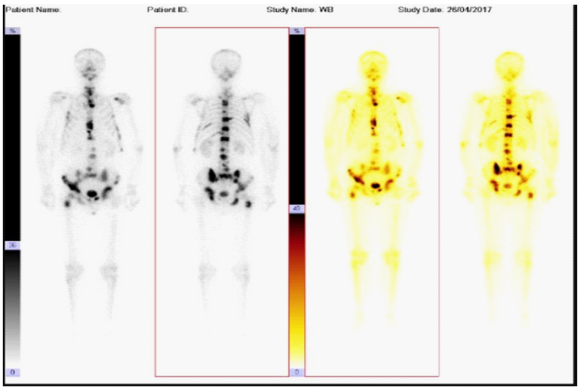

Figure 9: Pre-therapeutic whole-body bone scintigraphy in patient №2 - data on multiple hyperfixation foci corresponding to diffuse hematogenous dissemination in the spine, thorax and pelvis.

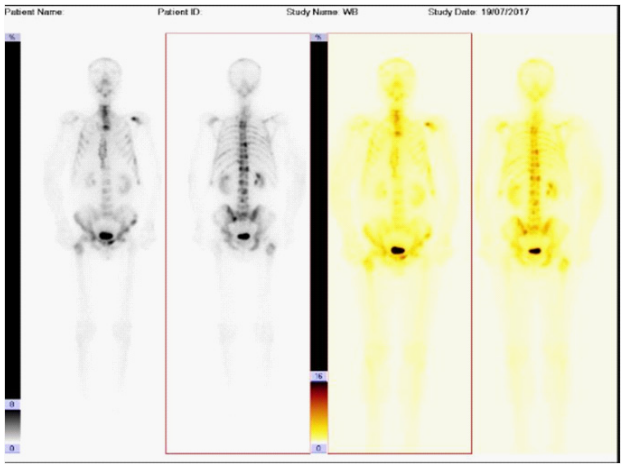

Figure 10: Control whole-body bone scintigraphy after the 4th application of 223 Radium in patient №2 - persistent hyperficial foci in the spine persist - with evidence of a decrease in the intensity of involvement, as well as a significant reversal of changes in the pelvic bones.

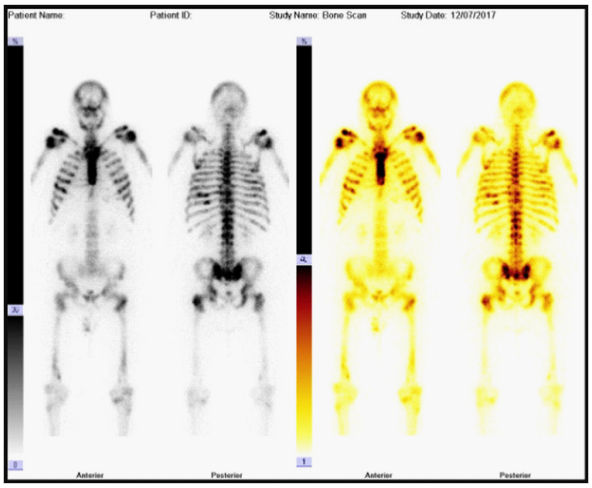

Figure 13: Control of whole-body bone scintigraphy after the 4th application of 223 Radium in patient №3 - new areas with increased fixation of RF in the sternum, sacroiliac joints, shoulder joints.

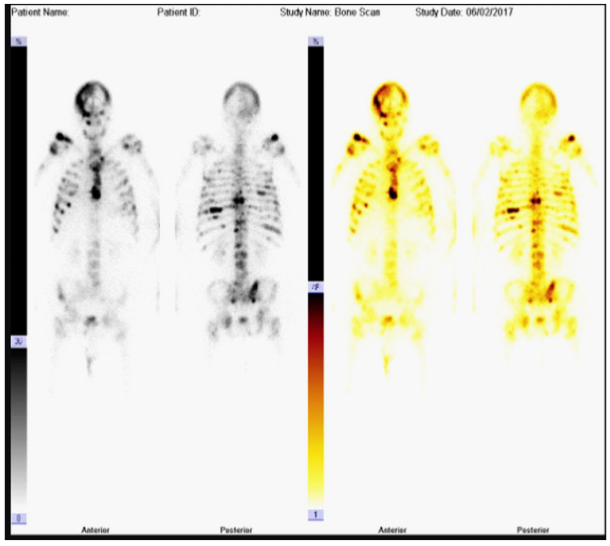

Figure 11: Pre-therapeutic whole-body bone scintigraphy in patient №3 - data for multiple areas with increased RF fixation in the skull, sternum, spine, bilateral ribs, right shoulder joint, pelvic bones.

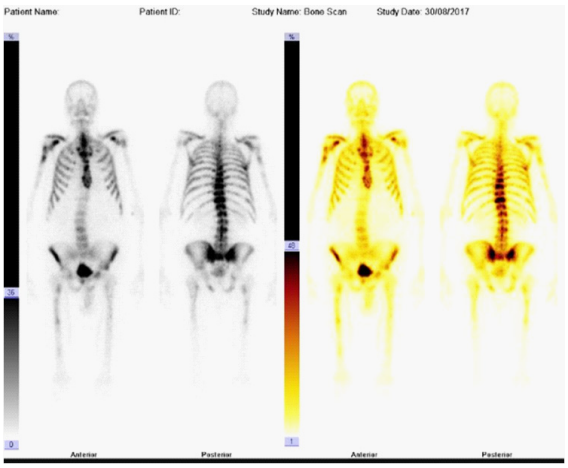

Figure 14: Pre-therapeutic whole-body bone scintigraphy in patient №4 - data for multiple areas with increased RF fixation in the spine, sacroiliac joints and sacrum, sternum, right humerus diaphysis, proximal metaphysis and right femur and iliac diaphysis, iliac as in advanced metastatic bone disease.

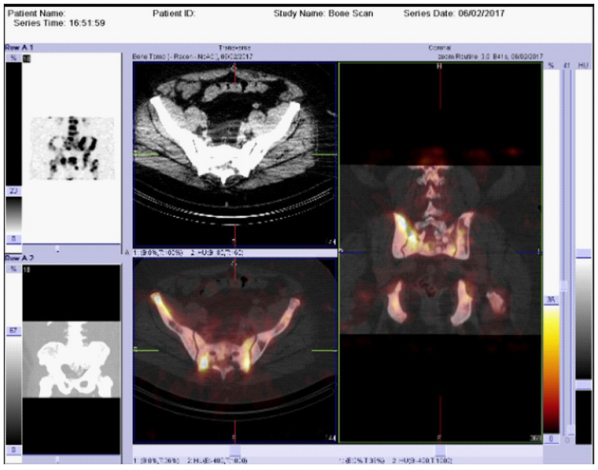

Figure 12: SPECT / CT of the pelvis in patient №3 - data for multiple areas with increased fixation of RF in the pelvic bones, which corresponds to diffuse sclerotic transformation.

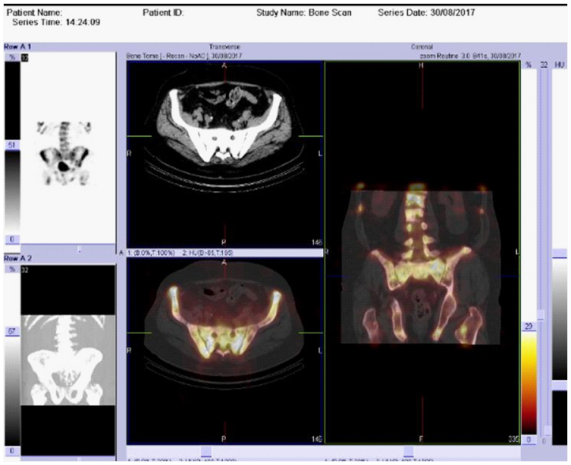

Figure 15: Pelvic SPECT/CT in patient №4 - data for multiple areas with increased RF fixation in the sacroiliac joints and sacrum, sternum, right humerus diaphysis, proximal metaphysis and right femur diaphysis, iliac and sciatic bones corresponding of diffuse sclerotic transformation of bone structures in these areas.

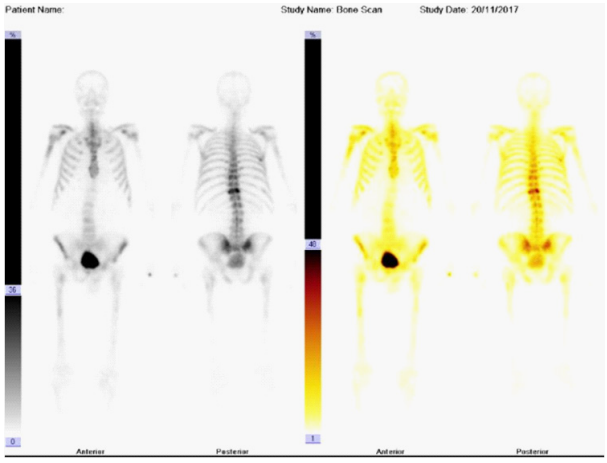

Figure 16: Control whole-body bone scintigraphy in patient №4 after the 4th application of 223 Radium, which shows a reduction in the number and intensity of RF involvement in bone lesions, with the presence of residual areas with increased fixation in Th 7-11, sacroiliac synchondrosis, sacrum, the proximal metaphyses of the right humerus and right femur, single foci in the sternum.

In March, 2016 a PET/CT with new prostate specific tracer (68 Ga labelled prostate specific membrane antigen, PSMA) was scheduled in order to further evaluate the reason for biochemical recurrence and discuss the need of a different treatment line. The results from the study objectively showed focal high tracer accumulation in the thoracic spine without underlying morphological alterations but highly suspicious for metastatic bone marrow involvement (Figure 7). Therefore, the patient was considered for radiotherapy of C7-Th5, combined with stereotactic body radiation of Th8 with a total radiation dose of 30 Gy. Still the PSA level was controlled unsatisfactorily and patient was referred for Radium-223 dichloride treatment. A total of four intravenous applications of Radium 223 dichloride were performed with average application activity of 39,6 MBq (55 кBq/кg). After the fourth application the patient was referred for a second 68 Ga PSMA PET/C Treassessment. The exam revealed total lesion regression with no disease related tracer accumulation (Figure 8). During the therapy course the serum PSA levels has been steady decreasing starting from 9.8 ng/ml to 1.53 ng/ml, 0.53 ng/ml, 0.18 ng/ml, 0.018 ng/ml until 0.00 ng/mlup to the present. There were no registered any significant hematological deviations nor other objective side effects. During the five years follow up the patient is still alive with no clinical or radiological progression.

The **second clinical case** is of a 50 years old patient with a high-risk low differentiated prostate cancer, Gleason score 9 (4+5), pT3N1M1, diagnosed in 2014 due to enlarged left supraclavicular lymph node. Since October, 2014 the patient was treated with denosumab, standard Antiandrogen Deprivation Therapy (ADT), Abiraterone acetate, Docetaxel with subsequent Cabazitaxel shift. Due to constantly elevating PSA up to 50.41 ng/ml, the patient was referred to Radium 223 dichloride therapy. For the time period 18.04-12.07.2017 the patient received 17,6 MBq 223 Radium /55 KBq/kg in total, with an average of 4,4 MBq per application (four intravenous applications). No significant blood count deviation or other side effects were present. During the 223 Radium therapy course the serum PSA levels showed the following dynamics: PSA – 80.25 ng/ml (04.2017), 42.54 ng/ml (05.2017), 284.2 ng/ml (06.2017) and 558.1 ng/ml (07.2017). After initial PSA decrease a subsequent abrupt elevation and biochemical progression was present in the course of treatment despite the relative improvement in tracer accumulation seen on the pretherapeutic and subsequent bone scan (Figures 9 & 10). A PET/CT with 68Ga PSMA PET/CT proved further additional dissemination in multiple regional and distant lymph nodes as well as pulmonary deposits. Radium 223 dichloride treatment was precluded due to soft tissue progression. The patient was referred to metabolic brachytherapy using another radiopharmaceutical (177 Lutetium PSMA) in a foreign center. At the time of writing this manuscript the patient had four applications of177 Lu PSMA with significant lymph node and tumor marker reduction and PSA levels of below 0,002 ng/ml. The patient died in 2019, respectively three years post last 223 Radium application but the exact reason for his last clinical deterioration is not documented in our hospital.

The **third clinical case** is of a 67 year old patient diagnosed with low-grade prostate cancer (pT3N0M0, PSA-60,5 ng/ml, Gleason score 8) in 2011 and secondary oligometastatic bone disease according to already performed bone scan. LHRH – agonist and non-steroid antiandrogen (bicalutamide) therapy was initiated with further administration of denosumab and bisphosphonate according to a scheme. Due to this therapy tumor marker level reached as low as 10 ng/ml and was in stable control for the next two years followed by another peak of PSA >120 ng/ml in correlation with several new bone lesions and pain symptoms. Docetaxel therapy was given as initial therapy but was not well tolerated. Since 2015 a therapy with Enzalutamide (160 mg per day) was initiated. After a short period of lucidity serum PSA reaches the extreme level of >1600 ng/ml while bone lesions had become diffuse. In the beginning of 2016 parallel mitoxantrone treatment starts which was well tolerated though no significant therapeutic effect was documented.

Due to pain symptom aggravation the patient was referred to 223 Radium therapy. For the time period 25.04-19.07.2017 were conducted four intravenous applications of a total of 35,2 MBq 223 Radium (55 KBq/kg., with patient body mass of 160 kg) and a mean of 8,8 MBq per application (for a total of four intravenous applications). Pretherapeutic whole-body bone scintigraphy is performed in combination with SPECT/CT (Figures 11 & 12) showing diffuse bone metastases.

During the treatment course with 223 Radiumblood count and serum PSA levels followed count changes as shown in Table 1.

As seen in Table 1 in the course of treatment the patient experienced significant hematology toxicity with grade II anemia and grade III thrombocytopenia, leading to a treatment suspension. Supportive therapy and blood transfusion were initiated in order to restore hematology components. Control bone scan revealed further progression (Figure 13).

Table 1: Blood counts and serum PSA levels in patient №3.

Date	PSA	Hb	Hct	RBC	PLT
18/04/2017	1900 ng/ml	140 g/L	33.5%	5.78 x 10^{12}/L	350 x 10^{9}/L
16/05/2017	1850 ng/ml	130 g/L	30.5%	3.36 x 10^{12}/L	140 x 10^{9}/L
13/06/2017	1600 ng/ml	95 g/L	28.5%	2.99 x 10^{12}/L	80 x 10^{9}/L
09/07/2017	1800 ng/ml	80 g/L	25.9%	2.5 x 10^{12}/L	40 x 10^{9}/L

Table 2: Blood counts and tumor marker levels in patient №4.

Date	PSA	Hb	Hct	RBC	APh
14/09/2017	111.2 ng/ml	117 g/L	33.5%	3.66 x 10^{12}/L	151 U/L
16/10/2017	96.86 ng/ml	107 g/L	30.5%	3.36 x 10^{12}/L	125 U/L
29/11/2017	105.1 ng/ml	95 g/L	28.5%	2.99 x 10^{12}/L	-
28/12/2017	122.4 ng/ml	88 g/L	25.9%	2.7 x 10^{12}/L	-

Six months after last 223 Radium application the PSA decreased up to 645.5 ng/ml from 1900 ng/ml and blood counts level were also improved (Hb-92 g/L, Plt-56x109/L). At the time of writing this manuscript the patient had no skeletal pain. The patient died in June 2018, respectively 11 months after the last 223 Radium application.

The **fourth clinical case** is of a 76 years old patient diagnosed with low-grade prostate cancer in 2010 with no data of distant metastatic sites according to bone and CT scan. There was shortage of data about initial tumor marker level. ADT with LHRH – agonist was initiated before. In 2015 the patient had Intensity-Modulated Radiation Therapy (IMRT) planning (total radiation dosage of 7000 cGy, daily radiation dosage of 200 cGy). In 2016 a metastatic bone disease was documented and therapy with Denosumab (120 mg per day) and Enzalutamide (160 mg per day) was initiated. The patient was referred to 223 Radium therapy because of severe skeletal pain and had four intravenous application of a total of 28,1 MBq 223 Radium (55 KBq/kg) with a mean of 5,6 MBqper application. Pretherapeutic whole-body bone scan combined with pelvic SPECT/CT was performed (Figures 14 & 15).

During the whole 223 Radium treatment hematology components and serum PSA levels were dynamically followed and listed as follows in Table 2.

After initial insignificant tumor marker decrease there was again abrupt elevation during the course of treatment. No significant deviations in neutrophil or thrombocyte levels were noteced, buta grade II anemia was registered. The objective results from the subsequent bone scan presented up to 80 % decrease in lesion number and radiopharmaceutical accumulation (Figure 16). Patient's subjective pain symptoms were also reduced and he was back to his daily activities. A further contrast enhanced CT scan revealed newly appeared bilateral adrenal lesions. The patient was then referred to 68 Ga PSMA PET/CT which further proved the soft tissue dissemination. The patient died in May 2018, five months after the last 223 Radium application but the exact reason and follow up history for this last period is missing since he has been no longer admitted to our hospital.

Discussion with review of the literature

Initial treatment of newly diagnosed metastatic prostate cancer includes medical or surgical castration. It is estimated that the disease becomes resistant to standard Androgen Deprivation Therapy (ADT) for a mean period of 18 months. Lethal cases are typically result of Metastatic Castration Resistant Prostate Cancer (mCRPC) with an average lifespan of two years [17].

Up to date the approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone/prednisolone, enzalutamide, cabazitaxel, olaparib and radium-223 [18]. Several prospective randomised phase 3 trials showed an OS benefit for first-line treatment in men with mCRPC. None of the control arms used in these trials is currently considered standard of care. Abiraterone, enzalutamide, and sipuleucel-T were evaluated as first-line agents in asymptomatic patients, docetaxel in both symptomatic and asymptomatic patients, and radium-223 dichloride (radium-223) in symptomatic patients with bone metastases [19]. Sipuleucel-T is only available in the USA. Nevertheless, all patients who receive first line treatment for mCRPC will eventually progress. High level evidence exists only for second-line treatments after first-line treatment with docetaxel and for third-line therapy. A positive example is the CARD trial which clearly established cabazitaxel as the better third-line treatment in docetaxel pre-treated patients after one ARTA compared to the use of a second ARTA [20]. In this setting, abiraterone, cabazitaxel, enzalutamide, and radium-223 have also shown an Overall Survival (OS) benefit [21,22]. Currently, most patients are treated with abiraterone or enzalutamide in the first-line setting and there is not a lot of prospective data on second or further-line treatment in these men.

Although, the number of effective treatments is increasing, head-to-head comparisons are still rare, as are prospective data assessing the sequencing of available agents. Therefore it is not clear how to select the most appropriate second-line treatment, in particular in patients without genetic alterations or other biomarkers. It is important that treatment decisions are individualised, therefore, clinical decisions should be based on a comprehensive evaluation of the patient's symptoms, presence of visceral metastasis, and Performance Status (PS) [4].

Among all disease related consequences metastatic bone disease is still the most challenging topic in men with mCRPC. Bone metastasis occurs in more than 90% of CRPC patients and is one of the main causes of death, disability, poorquality of life, and high treatment costs [22]. Complications include significant bone pain, skeletal-related complications such as pathologic fractures, malignant hypercalcemia, bone marrow suppression, and spinal cord compression. Unfortunately, all currently available bone targeting agents (bisphosphonates, RANK ligand inhibitors) are mainly implemented as palliative and supporting care purposes for bone loss protection and prevention of skeletal-related events without any improvement in overall survival. Although traditional forms of External Beam Radiation Therapy (EBRT) are effective for palliation, many patients present concurrently with painful lesions in several distinct areas of the skeleton and a systemic approach is often necessary.

Over the past few decades, several radiopharmaceuticals have been developed with bone-seeking properties that provide palliation of pain to multiple areas of the skeleton simultaneously without the significant soft-tissue toxicity and technical complications of large-field EBRT. Most of them are beta-emitters (89 Strontium, 153 Samarium), releasing highly energetic electrons that deposit their energy over up to several millimetres in the surrounding tissues. However, the energies of emitted beta particles are generally not sufficient to elicit a significant cytotoxic response [23].

Radium-223 dichloride (radium-223) is the first generation targeted alpha emitter that selectively binds to are as of increased bone turnover in bonemetastases and emits high-energy alphaparticles of short range (<100 μm) [24]. As a bone-seeking calciummimetic, radium-223 is bound into newly formed bonestroma, especially with in the microenvironment of osteoblastic or sclerotic metastases [12]. The high-energy alpha-particle radiation induces mainly double-stranded DNA breaks that result in a potent and highly localised cytotoxic ef-

fect in the target are as [25]. Unlike beta particles, shorter run of alpha particles minimizes toxic effects on adjacent healthy tissue.

Radium-223 dichloride has been approved by EMA in 2013 for treatment of patients with mCRPP and symptomatic bone metastases based on the results from a phase 3, randomised, double-blind, placebo-controlled, multicenter phase III trial ALSYMPCA (Alpharadinin SYMptomatic Prostate C Ancerpatients) [24].

The first application of Radium-223 dichloridein Bulgaria was in our university hospital centre. For one year period 223 Radium therapy was applied on four consequtive patients with bonemetastases from CRPC. The small number of patients owes to the fact that the therapy was still not included into the national health insurance fund's reimbursement list. Three out of our patients (2,3 and 4 clinical case) were admitted to the departmental ready having advanced bone involvement (>20 bone lesions), pain symptoms and high tumor marker. Case 1 patient was oligometastatic (<6 bone lesions), with outpain symptoms and relatively low tumor marker. Two out of our patients (case 2 and 3) had previous chemotherapy. All patients conducted simultaneous therapy with standard and new generation ARTA.

Currently, the approved therapeutic regimen of 223 Radium includes up to six consecutive applications in 28 days intervals. All of our patients had insufficient therapeutic course of three to four intravenous applications of 223 Radium. According to the recently consensus recommendations the treatment in mCRPC should not be stopped for PSA progression alone. Instead, at least two of the three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled [26]. In our first patient the treatment was interrupted after the fourth cycle by his own will because of full biochemical and radiological response. The reason for treatment interruption in the rest of the patients was biochemical and visceral disease progression in the second patient, biochemical and radiological bone progression in the third patient and visceral progression in the fourth patient. Additional arguments for the therapy interruption in two of the patients was the registered haematological deterioration (grade II anaemia and grade III thrombocytopenia in one patient and grade II anaemia in the other patient). In general, Radium-223 has been reported to have a favourable safety profile, with minimal myelotoxicity, in phase 1 and 2 studies involving patients with bone metastases [16]. In ALSYMPCA trial the hematologic and nonhematologic adverse events that occurred were in at least 5% of patients in either study group with the most common adverse haematological reactions (≥5%) including anaemia (31%), thrombocytopenia (12%) and neutropenia (5%) [24]. For comparison, in TROPIC trial chemotherapy with cabazitaxel is associated with significant immunosuppression including all stages of neutropenia (94%), leucopenia (96%), anemia (97%) and thrombocytopenia (47%) [27]. Neutropenia is also a common result in patients treated with docetaxel [6].

The relatively high frequency of haematological decline in our patients could be explained by the diffuse initial bone involvement and borderline bone marrow reserve in most of them. This further implicates the need for careful tailoring the therapeutic regimen and assessment of the right timing for initiation of this therapy in such cases.

All patients in our group tolerated the therapy well with little or no subjective complains except for mild fatigue in two patients. In addition, all patients reported improvement in the quality of life with complete resolve of the painful symptoms by the end of the treatment. The last was also valid for the third patient with initially poor performance (ECOG) status. These results was in accordance with the previously reported as a significantly higher percentage of patients who received radium-223, as compared with those who received placebo, had a meaningful improvement in the quality of life according to the FACT-P total score [24].

The objective therapy response in our case series was evaluated by control radiological exam (bone scan or PET/CT) conducted after the last 223 Radium application. Complete metabolic and morphological response was reported only in our first patient which corresponds very well with his clinical remission during the five years follow up. In the second and the fourth patient was registered "partial" metabolic response but clear biochemical and soft tissue progression during the treatment course. This corresponds well with the short survival of less than 12 months, especially in our fourth patient who did not perform any further treatment.

In the current guidelines 223 Radium has been readily recommended as a second line treatment form CRPC with symptomatic bone metastases and no visceral dissemination only after unsuccessful (progression) firstline treatment [4]. Due to safety concerns, use of radium-223 was recently restricted to after docetaxel and at least one ARTA agent [28]. In particular, the use of radium-223 in combination with abiraterone acetate plus prednisolone showed significant safety risks related to fractures and more deaths [29]. This was most striking in patients without the concurrent use of anti-resorptive agents. Patients with disease progression and low performance status (PS ≥ 2) mainly due to symptomatic bone metastases could be an exception [16]. In such cases as well as in patients who refuse standard do cetaxel chemotherapy 223 Radium can be used as a first choice treatment method.

Despite the small number, our case studies are in line with the results from previous trials which show significant but largely variating survival benefit (from five months to 5 years) compared to placebo irrelevant of the presence of previous docetaxel or opiate therapy [16,30]. This may indicate that severity of symptoms should not play a leading role in decision making whether to initiate 223 Radium therapy or not. Early application may be justified also in cases of minimal or mild symptomatic as it is in cases of severe pain symptoms. Factors associated with improved OS and therapy efficacy include performance status ECOG 0-1, fewer than 6 bone metastases, normal alkaline phosphatase level and no prior chemotherapy use [31]. The current clinical practice shows that the application of 223 Radium in later stages, when 20 or more bone lesions are present, is not that effective and associated with higher frequency of myelosuppression. The significant baseline predictors for grade 2-4 hematologic toxicities related to radium-223 treatment are the extent of disease (6-20 vs.< 6 bone metastases), elevated prostate-specific antigen for anaemia and prior docetaxel, decreased haemoglobin, decreased platelets for thrombocytopenia, respectively [32]. This is also in line with the results in our third patient, whom initial bone marrow involvement was extremely extensive, with documented radiological and biochemical progression right after the fourth course and subsequent survival less than 11 months. On the contrary in our first patient with less than 6 bone lesions there was a complete morphological and biochemical response with no haematologi-

cal deviations.

Some of these results may change the paradigm about when is optimal to initiate 223 Radium therapy in the direction of an earlier start point including patients with radiologically proven bone metastases with no or minimally expressed symptoms. Usually, treatment with 223 Radium treatment starts when clinical condition worsens and chemotherapy is inevitable. Nevertheless, after chemotherapy patients are less likely to tolerate another treatment line due to immunosuppression and concomitant side effects. That is the reason why in some clinical situations 223 Radium application could be preferred before standard chemotherapy allowing for the whole therapeutic course to be conducted. That includes six intravenous drug administration's which are proven to be more effective on overall survival reducing the number of cases needing interruption because of side effects [33]. In addition, the subgroup analysis of patients of ALSYMPCA demonstrates a possibility for another therapeutic options and good chemotherapy tolerance after 223 Radium treatment.

Conclusion

Despite small patient number and non-linear first results form 223 Radium application in Bulgaria the latter give hope for effective future practice according to the data for complete or partial morphological response as well as complete improvement of pain symptoms and quality of life in all treated patients treated. In the future we expect that all patients with mCRPC and proven bone metastases would be able to receive 223 Radium treatment routinely after first line antiandrogen and/or chemotherapy.

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